

What is claimed is:

1. A method of diminishing or abrogating SMAD activity comprising the step of
5 contacting a cell with an agent that stimulates or enhances TAK1 expression, wherein TAK1 interacts with an MH2 domain of a SMAD protein, thereby diminishing or abrogating SMAD activity.
2. A method of stimulating or enhancing SMAD activity comprising the step of
10 contacting a cell with an agent that diminishes or abrogates TAK1 interaction with an MH2 domain of a SMAD protein, thereby stimulating or enhancing SMAD activity.
3. The method of claim 2, wherein said agent competes for endogenous TAK1.
- 15 4. The method of claim 2, wherein said agent is a nucleic acid.
5. The method of claim 4, wherein said nucleic acid corresponds to or is at least 70 % homologous to SEQ ID No: 1 or SEQ ID No: 2.
- 20 6. The method of claim 2 wherein diminution or abrogation of TAK1 interaction with said MH2 domain of a SMAD protein is effected via diminishing or abrogating TAK1 expression or activity.
7. A method of stimulating or enhancing BMP-mediated SMAD activity comprising
25 the step of contacting a cell with an agent that diminishes or abrogates TAK1 expression or function.
8. The method of claim 7, wherein said agent functions to prevent TAK1 interaction with a SMAD MH2 domain.
- 30 9. The method of claim 7, wherein said agent competes for endogenous TAK1.

10. The method of claim 7, wherein said agent is a nucleic acid.

11. The method of claim 10, wherein said nucleic acid corresponds to or is at least 70 % homologous to SEQ ID Nos: 1 or 2.

12. The method of claim 10, wherein said nucleic acid is expressed from an expression vector.

13. A method of diminishing or abrogating BMP-mediated SMAD activity comprising the steps of contacting a cell with an agent that stimulates or enhances TAK1 expression or function.

14. The method of claim 13, wherein said agent functions to facilitate or enhance TAK1 interaction with a SMAD MH2 domain.

15. The method of claim 13, wherein said agent is a nucleic acid.

16. The method of claim 15, wherein said nucleic acid is expressed from an expression vector.

17. The method of claim 13 wherein said SMAD activity is mediated via BMP-2.

18. A method of enhancing osteogenesis in a subject in need, comprising the steps of contacting a cell with osteogenic potential in said subject with an agent that mitigates or abrogates TAK1 expression or function, thereby enhancing osteogenesis in said subject.

19. The method of claim 18, wherein said agent mitigates or abrogates TAK1 expression or function following TAK1 activation by proinflammatory cytokines.

20. The method of claim 19, wherein said proinflammatory cytokines are IL-1 or TNF-alpha.

21. The method of claim 18, wherein said agent competes for endogenous TAK1.

22. The method of claim 18, wherein said agent is a nucleic acid.

5 23. The method of claim 18, wherein said nucleic acid corresponds to or is at least 70 % homologous to SEQ ID Nos: 1 or 2.

24. The method of claim 18, wherein said cell with osteogenic potential is a mesenchymal stem cell, a progenitor cell, an osteoblast, or any cell capable of
10 differentiating into an osteoblast.

25. The method of claim 18, wherein said cell with osteogenic potential is at a site of inflammation in said subject.

15 26. The method of claim 18, wherein said subject suffers from inflammation-mediated bone loss.

27. The method of claim 25, wherein said subject suffers from periodontal disease, osteoarthritis, Köhler's bone disease, rheumatoid arthritis or osteoporosis.

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28. A method of enhancing osteogenesis in a subject in need, comprising the steps of :

(i) genetically engineering a cell with osteogenic potential to be deficient in TAK1 expression or function; and

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(ii) administering said engineered cell to said subject in need;

thereby enhancing osteogenesis in said subject.

29. The method of claim 28, wherein said cell is further engineered to express a growth
30 factor for stimulating or enhancing osteogenesis.

30. The method of claim 28, wherein said growth factor is a bone morphogenic protein.

31. The method of claim 28, wherein said cell is further engineered to express a product that competes for endogenous TAK1.
- 5 32. The method of claim 28, wherein said product prevents TAK1 expression.
33. The method of claim 28, wherein said product prevents TAK1 kinase activity.
- 10 34. The method of claim 28, wherein said cell is genetically manipulated via the introduction of a nucleic acid corresponding to or at least 70 % homologous to SEQ ID Nos: 1 or 2.
- 15 35. The method of claim 28, wherein said cell with osteogenic potential is a mesenchymal stem cell, a progenitor cell, an osteoblast, or any cell capable of differentiating into an osteoblast.
36. The method of claim 28, wherein said cell with osteogenic potential is loaded on a scaffolding material, prior to administering said cell to said subject in need.
- 20 37. The method of claim 28, wherein said cell is administered to a site of inflammation in said subject.
38. The method of claim 28, wherein said subject suffers from inflammation-mediated bone loss.
- 25 39. The method of claim 28, wherein said subject suffers from periodontal disease, osteoarthritis, Köhler's bone disease, rheumatoid arthritis or osteoporosis.
- 30 40. A method of enhancing bone repair in a body of a subject in need comprising the steps of contacting a cell with osteogenic potential in said subject with an agent that mitigates or abrogates TAK1 expression or function, thereby enhancing bone repair in a body of said subject.

41. The method of claim 40, wherein said agent mitigates or abrogates TAK1 expression or function following TAK1 activation by proinflammatory cytokines.
- 5 42. The method of claim 41, wherein said proinflammatory cytokines are IL-1 or TNF-alpha.
43. The method of claim 40, wherein said agent competes for endogenous TAK1.
- 10 44. The method of claim 40, wherein said agent is a nucleic acid.
45. The method of claim 40, wherein said nucleic acid corresponds to or is at least 70 % homologous to SEQ ID Nos: 1 or 2.
- 15 46. The method of claim 40, wherein said cell with osteogenic potential is a mesenchymal stem cell, a progenitor cell, an osteoblast, or any cell capable of differentiating into an osteoblast.
47. The method of claim 40, wherein said cell with osteogenic potential is at a site of
20 inflammation in said subject.
48. The method of claim 40, wherein said subject suffers from inflammation-mediated bone loss.
- 25 49. The method of claim 48, wherein said subject suffers from periodontal disease, osteoarthritis, Köhler's bone disease, rheumatoid arthritis or osteoporosis.
50. A method of enhancing bone repair in a subject in need, comprising the steps of :
- 30 (i) genetically engineering a cell with osteogenic potential to be deficient in TAK1 expression or function; and
(ii) administering said engineered cell to said subject in need;

thereby enhancing bone repair in said subject.

51. The method of claim 50, wherein said cell is isolated from the body of said subject in
5 need, prior to genetic engineering.

52. The method of claim 50, wherein said cell is further engineered to express a growth
factor for stimulating or enhancing osteogenesis.

10 53. The method of claim 52, wherein said growth factor is a bone morphogenic protein.

54. The method of claim 50, wherein said cell is further engineered to express a product
that competes for endogenous TAK1.

15 55. The method of claim 50, wherein said product prevents TAK1 expression.

56. The method of claim 50, wherein said product prevents TAK1 kinase activity.

57. The method of claim 50, wherein said cell is genetically manipulated via the
20 introduction of a nucleic acid corresponding to or at least 70 % homologous to SEQ ID
Nos: 1 or 2, or a fragment thereof.

58. The method of claim 50, wherein said cell with osteogenic potential is a
mesenchymal stem cell, a progenitor cell, an osteoblast, or any cell capable of
25 differentiating into an osteoblast.

59. The method of claim 50, wherein said cell with osteogenic potential is loaded on a
scaffolding material, prior to administering said cell to said subject in need.

30 60. The method of claim 50, wherein said cell is administered to a site of inflammation
in said subject.

61. The method of claim 50, wherein said subject suffers from inflammation-mediated bone loss.

62. The method of claim 50, wherein said subject suffers from periodontal disease, osteoarthritis, Köhler's bone disease, rheumatoid arthritis or osteoporosis.

63. A method of suppressing osteogenesis in a subject in need, comprising the steps of contacting a cell with osteogenic potential in said subject with an agent that stimulates or enhances TAK1 expression or function, thereby suppressing osteogenesis in said subject.

64. The method of claim 63, wherein said cell with osteogenic potential is a mesenchymal stem cell, a progenitor cell, an osteoblast, or any cell capable of differentiating into an osteoblast.

65. The method of claim 63, wherein said cell with osteogenic potential is at a site of lung injury or persistent infection.

66. A method for the identification of candidate gene products involved in downstream events in BMP-mediated SMAD activity resulting in osteogenesis, comprising:

- (i) introducing an agent that inhibits or abrogates TAK1 binding to SMAD MH2 domains into a cell with osteogenic potential;
- (ii) culturing a cell with osteogenic potential as in (a), without said agent;
- (iii) separately harvesting RNA from each cell following stimulation of BMP-mediated SMAD activity; and
- (iv) assessing differential gene expression,

wherein differentially expressed genes in (a) as compared to (b) indicates that the gene is involved in downstream events in BMP-mediated SMAD-signaling resulting in osteogenesis.

67. A method for the identification of an agent involved in stimulating or enhancing osteogenesis, comprising:

- 5 (a) Contacting a cell with osteogenic potential with an agent thought to inhibit or abrogate TAK1 interaction with SMAD MH2 domains;
(b) culturing said cell with osteogenic potential under conditions facilitating TAK1-SMAD MH2 interaction; and
(c) determining whether said agent altered said TAK1-SMAD MH2
10 interaction,

wherein altered TAK1-SMAD MH2 interaction as a result of contact with said agent produces stimulated or enhanced osteogenesis; thereby identifying an agent involved in stimulating or enhancing osteogenesis.

15 68. An isolated nucleic acid, wherein said nucleic acid is as set forth in SEQ ID Nos. 1 or 2.

69. The isolated nucleic acid of claim 68, wherein said nucleic acid is at least 70 % homologous to SEQ ID Nos: 1 or 2.

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70. A vector comprising the isolated nucleic acid of claim 68.

71. The vector of claim 70, further comprising a promoter for regulating transcription of the isolated nucleic acid in sense or antisense orientation.

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72. The vector of claim 70, further comprising positive and/or negative selection markers for selecting for homologous recombination events.

73. A host cell or animal comprising the vector of claim 70.

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74. The host cell of claim 73, wherein said cell is prokaryotic or eukaryotic.

75. The host cell of claim 73, wherein said cell is a mesenchymal stem cell, a progenitor cell, an osteoblast, or any cell capable of differentiating into an osteoblast.

76. An isolated nucleic acid sequence, wherein said nucleic acid sequence is antisense to
5 the nucleic acid sequence as set forth in SEQ ID Nos: 1 or 2, or a fragment thereof.

77. A vector comprising the isolated nucleic acid of claim 76.

78. The vector of claim 77, further comprising a promoter for regulating transcription of
10 the isolated nucleic acid, and/or further comprising positive and/or negative selection markers for selecting for homologous recombination events.

79. A host cell or animal comprising the vector of claim 77.

80. The host cell of claim 79, wherein said cell is prokaryotic or eukaryotic.
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81. The host cell of claim 79, wherein said cell is a mesenchymal stem cell, a progenitor cell, an osteoblast, or any cell capable of differentiating into an osteoblast.

82. An oligonucleotide of at least 12 bases specifically hybridizable with the isolated
20 nucleic acid of SEQ ID Nos: 1 or 2.

83. The oligonucleotide of claim 82, wherein said oligonucleotide is in either sense or
antisense orientation.
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84. The oligonucleotide of claim 82, wherein said oligonucleotide is either single or
double-stranded.

85. The oligonucleotide of claim 82, wherein said oligonucleotide corresponds to, or is
30 at least 70 % homologous to SEQ ID Nos: 3 or 4.

86. A composition comprising the oligonucleotide of claim 82.